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The Influence of age on sensitivity to Dexmedetomidine sedation during Spinal Anaesthesia in Infra Umbilical Surgeries

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Abstract
Background: Dexmedetomidine is a highly selective alpha 2 adrenergic receptor agonist that has been used for sedation under spinal anaesthesia. The aim of this study was to evaluate the influence of age on sensitivity to dexmedetomidine sedation in adult patients scheduled for infra umbilical surgery under spinal anaesthesia to identify dexmedetomidine ED50 for adequate sedation among different age groups.
Material & Method: In this study, 90 patients of ASA grade I and II, between 18-79 years of age scheduled for infra umbilical surgery under spinal anaesthesia were recruited and randomly allocated into three age groups (30 in each) young age group (18-40yrs), middle-age groups (41-60yrs) and elderly age group (61-79yrs). After a spinal anaesthesia loading dose of dexmedetomidine @ 1mcg/kg for the young and middle age group and 0.7mcg/kg for the elderly age group was administered over 15 minutes. Dixon's up-and-down method was used to determine the ED50 of the drug for adequate sedation. We assessed the depth of sedation with the Ramsay sedation scale and measured vital signs and oxygen saturation.
Result: ED50 in the elderly group was lower than the other 2 groups (elderly: 0.66 ± 0.04; middle aged: 0.80 ± 0.07; young: 1.12 ± 0.06μg/kg; both P < .001). Bradycardia and Hypotension were more common in elderly patients.
Conclusion: Elderly patients are more sensitive to dexmedetomidine sedation as compared to younger patients

Keywords: Dexmedetomidine, infra umbilical surgery, Spinal anaesthesia

Introduction
Nowadays Subarachnoid block is the most widely used regional anaesthesia modality for infra umbilical surgical procedures. Regional anaesthesia, over general anaesthesia, has many advantages like consciousness, intact spontaneous breathing, patent airway during surgical procedures [1, 2]. During the surgical procedures, consciousness is the main cause of the Patient's anxiety and dissatisfaction, fear of being awake during the surgery, fear of needle prick, fear of numbness are some of the major factors for refusal of spinal anaesthesia by the patients. Some other factors like awkward positioning, cold environment of Operation theatre, and remaining in the same position for a longer duration also increase patients' anxiety and reduce patients' satisfaction with anaesthesia care [3]. During spinal anaesthesia, adequate sedation will relieve the patient's anxiety, psychological and physiological stress and increase the satisfaction of both patient and surgeon [4, 5]. Dexmedetomidine is a potent and highly selective alpha-2 receptor agonist, has been safely used to sedate patients under regional anaesthesia [6-8]. The elimination half-life of dexmedetomidine is 2-3 hours. Dexmedetomidine acts on presynaptic alpha-2 receptors located on locus ceruleus, which is a predominant nucleus of the brain stem and responsible for the regulation of sleep and respiratory control [9]. Postsynaptic activation in the central nervous system inhibits sympathetic activity which results in a decrease in heart rate and blood pressure. Also, infusion of dexmedetomidine causes activation of alpha-2 receptors at the spinal cord resulting in inhibition of nociceptive impulse transmission. As compared to other sedatives like midazolam and propofol, dexmedetomidine has easy arousal, and minimal respiratory depression [10, 11], and better cognitive functions postoperatively. Also, intravenous dexmedetomidine causes early-onset and prolongation of the duration of spinal anaesthesia

[12-14]. Usually, dexmedetomidine is given as a bolus dose initially and after that as a continuous infusion. To achieve adequate sedation a single dose of dexmedetomidine can also be given for short surgical procedures under spinal anaesthesia [8, 12-16]. Dexmedetomidine has dose-dependent side effects like bradycardia and hypotension [17-20] that's why dose adjustment is required to avoid these side effects. Because of the higher incidence of bradycardia and hypotension in elderly patient's dose reduction is recommended. Considering all these facts, elderly patients require lower doses of sedatives as compared with younger age groups patients to achieve the same level of sedation.

Aims and objectives

To investigate the influence of age on sensitivity to dexmedetomidine sedation in adult patients, scheduled for infra umbilical surgeries under spinal anaesthesia. To identify the dexmedetomidine ED50 for adequate sedation among different age groups.

Methodology

This study was approved by the institutional scientific and ethics committee.

Written informed consent was obtained from patients scheduled for elective infra umbilical surgery.

Inclusion criteria

American Society of Anaesthesiologists physical status I & II, Written informed consent from the patient or the relatives of the participating patient, Age group 18-79yrs.

Exclusion criteria

Patient's refusal, History of neurologic deficits**,** Coagulation disorders, Congestive heart failure or arrhythmias, bundle-branch block, Severe liver and kidney dysfunction, Pregnancy, Sensory block level over T-6, Patients who had recently received antidepressant treatment, or dementia.

Study design: A prospective randomized study.

Sample Size: Total 90 adult patients scheduled for elective infra umbilical surgery under spinal anaesthesia.

Patients were randomly allocated into 3 groups based on age:

1. Young group (patients 18–40 years of age)
2. Middle-aged group (patients 40–60 years of age)
3. Elderly group (patients 61–79 years of age).

Study Centre: MGM Medical College and MY Hospital, Indore (MP)

Procedure planned

After the arrival of the patient in the operating room, an intravenous (IV) cannula of 18 gauge, was secured and preloaded with 10-15ml/kg of ringer lactate infusion before spinal anaesthesia. Inj. Ondansetron 0.1mg/kg was given as premedication 30 min. before the surgery as per the institutional protocols and no sedative or analgesic was given before dexmedetomidine. Electrocardiogram, pulse rate, blood oxygen saturation (Spo2), respiratory rate, and noninvasive blood pressure were monitored. Spinal anaesthesia was performed with quincke's spinal needle of 25 gauge at L3/L4 level in a sitting position under full aseptic precaution. After confirmation of cerebrospinal fluid free flow, 0.5% hyperbaric bupivacaine with a dose of 0.3mg/kg was administered intrathecally over 10-15 seconds. The dermatomal extension of the sensory block was determined by cutaneous finger pinching every 5 minutes and the patient's position was adjusted to ensure that the upper block level was below T-8. Supplemental oxygen via a Venturi mask at 3 L/min was administered throughout the surgery. Dexmedetomidine was prepared as a 50 mL solution of 2µg/mL in 0.9% normal saline. The pre-calculated amount of dexmedetomidine solution was administered as continuous infusions using a syringe pump over 15 minutes. The initial dexmedetomidine dose was 1.0µg/kg in the young and middle-aged groups and 0.7µg/kg in the elderly group. Different doses were used because of safety issues in the elderly group, but these should not affect the results because the doses are adjusted according to the actual patient's reactions. It was administered by the anaesthetist responsible for the patients during surgery. Based on pilot testing and another previous study [10], which showed that when dexmedetomidine, as dosed, was expected to have a maximal effect around 26 minutes, that's why the 26-minute time point was selected to assess the effect of dexmedetomidine.

Adequate sedation was defined as an RSS score of 3 and above. If the adequate sedation level was not achieved, the dose for the next patient was increased by 0.05µg/kg. If the desired sedation was achieved, the dose is decreased by 0.05µg/kg for the next patient of the same group according to the Dixon up–and–down method. Heart rate (HR), SBP, DBP, mean arterial blood pressure (MAP), respiratory rate, and spo2 were recorded every 5 minutes up to 20 minutes and then every 10 minutes Intraoperatively and at the end of surgery. Bradycardia was defined as heart rate <55 bpm and treated within. Atropine 0.01mg/kg IV. For hypotension (mean blood pressure below 50 mm Hg) Ephedrine 6 mg and Ringer's lactate 5 mL/kg were administered. Hypertension was defined as a systolic blood pressure >160 mm Hg or a diastolic blood pressure >100 mm Hg. Rescuing procedures were reassessed every 1 minute. If Spo2 dropped below 90%, lightly tapping on the shoulder or mild shaking with a verbal prompt was performed.

Statistical analysis

The data was initially entered into the customized proforma designed for the study. Then this data was transferred to Microsoft Excel for analysis. Statistical Software Mini Tab Version 17.0 was used for calculating the P-values. Comparison of means among the three age groups was done using one-way ANOVA followed by Post-hoc Tukey test, the association between two nonparametric variables was done using Pearson chi-square test. A p-value < 0.05 was taken as statistically significant. The final data was presented in the form of tables and graphs.

Observations and results

Table 1: Comparison of the mean requirement of dexmedetomidine among the three groups at different time intervals

Parameter	Group	No.	Mean±SD	F value	P-value	Post-hoc Turkey		
						Young age group to middle age group	Young age group to elderly age group	Middle Age group to elderly age group
Dexmedetomidine Requirement	Young age group	30	1.12±0.06	525.821	0.000*	0.000*	0.000*	0.000*
	Middle age group	30	0.80±0.07					
	Elderly patients	30	0.66±0.04					

One-Way ANOVA followed by Post-hoc Turkey test applied. P-value = 0.000, highly significant

The mean dexmedetomidine requirement in the young age group was 1.12 ± 0.06, in the middle age group it was 0.80 ± 0.07 and in the elderly patients, it was 0.66 ± 0.04. The highest requirement of dexmedetomidine was in the young age group and the lowest was in the elderly patient's group.

Table 2: Comparison of mean Ramsey sedation score among the three groups at different time intervals

Parameter	Group	No.	Mean±SD	F value	P-value	Post-hoc Turkey		
						Young age group to middle age group	Young age group to elderly age group	Middle age group to elderly Age group
Ramsey Sedation Score	Young age group	30	3.03±0.93	0.237	0.789, NS	0.991, NS	0.861, NS	0.792, NS
	Middle age group	30	3.07±1.05					
	Elderly patients	30	2.90±0.99					

One-Way ANOVA followed by Post-hoc Turkey test applied. P-value = 0.000, highly significant

The mean Ramsey Sedation Score in the young age group was 3.03 ± 0.93, in the middle age group it was 3.07 ± 1.05 and in the elderly patients, it was 2.90 ± 0.99. Ramsey Sedation score was highest in the middle age group and lowest in the elderly age group patients.

Table 3: Comparison of side effects among the three groups

Side Effects	Young age group	Middle age group	Elderly age group	Total
None	27 90.0%	25 83.3%	23 76.7%	75 83.3%
Bradycardia	3 10.0%	5 16.7%	7 23.3%	15 16.7%
Total	30 100.0%	30 100.0%	30 100.0%	90 100.0%

Pearson chi-square value = 1.920, DF =2, p-value = 0.383, Not significant
In the young age group, 3 (10.0%) patients had bradycardia.
In the middle age group, 5 (16.7%) patients had bradycardia.
In the elderly patient's group, 7 (23.3%) patients had bradycardia.

A higher incidence of bradycardia was seen in the elderly age group patients, while the lowest was seen in the young age group patients. The association between the side effects and the groups was found to be statistically not significant (p=0.383), showing that the groups are independent of the side effects.

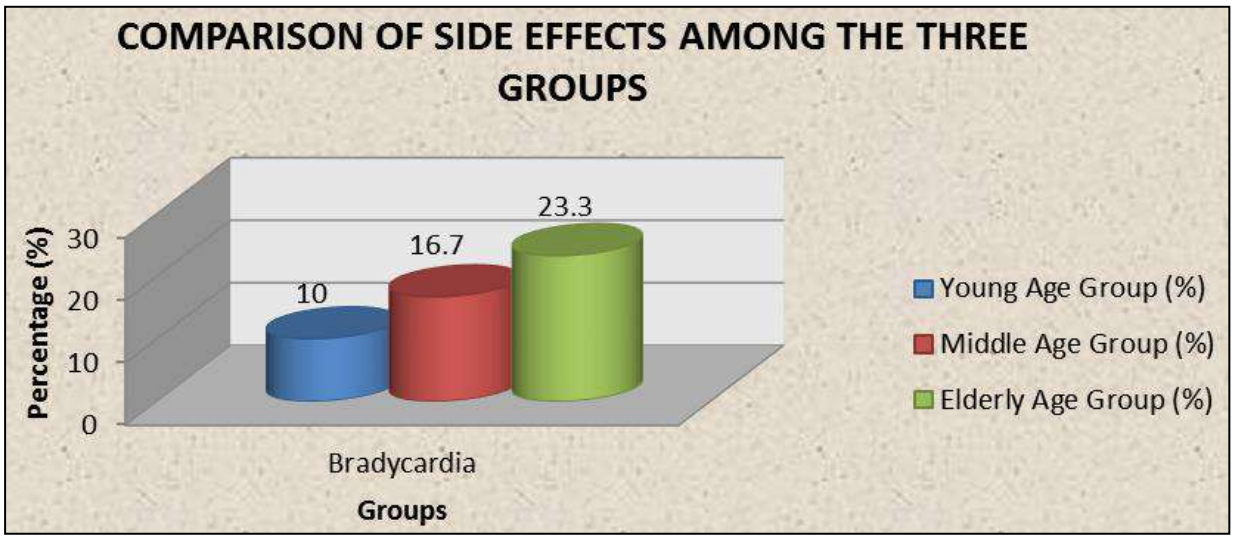

Fig 1: Bar diagram showing a comparison of side effects among the three age groups

Discussion

In this study, 90 patients of age groups 18 – 79 years, of either sex or ASA grade I & II, posted for elective infra umbilical surgeries were included. The patients were divided into three groups based on age; young age group (18-40 years), middle-age group (41-60years), and elderly age group (61-79 years).

The primary objective of this study was to assess the ED50 of dexmedetomidine in three different age groups to achieve the same level of sedation. It was found that the ED50 of dexmedetomidine to provide adequate sedation in patients of the elderly age group was less as compared to patients of younger and middle age groups. The age-associated increase in pharmacodynamics sensitivity to dexmedetomidine occurred due to a decrease in neuronal composition, neuron number, and neuronal regeneration capacities with age in the central nervous system [21].

A similar study was done by Xu, Bo MD, *et al.* [25] in adult patients in lower limb orthopedic surgery under spinal anesthesia. They also found that the ED50 in elderly patients was lower than younger age patients (ED50 of dexmedetomidine was 1.21±0.06 and 0.88±0.07mcg/kg for the young and elderly groups, respectively) while in our study the ED50 for the young age group was 1.12±0.06 and in the elderly patients it was 0.66±0.04mcg/kg. This difference may be due to differences in age groups. In their study, they selected young age groups between 18-39 years, middle age groups between 40-64 years, and elderly groups between 65-79 years. While in our study we selected young age groups between 18-40 years, middle age groups between 41-60 years, and elderly between 61-79 years.

In 2013, Song J, *et al.* [6], concluded that Intravenous dexmedetomidine with a loading dose of 1 µg/kg followed by continuous infusion at the rates of 0.25, 0.50, or 0.75µg/kg/hr produced adequate levels of sedation. There was an increased tendency of hypotension as the dose increased. To minimize the risk of hemodynamic instability, a dose of 0.25µg/kg/hr may be the most appropriate for continuous infusion of dexmedetomidine. In our study, we administered a loading dose of dexmedetomidine (1mcg/kg for the young and middle age group and 0.7mcg/kg for the elderly age group) for 15 minutes only no continuous infusion was given and we found no significant hemodynamic instability.

The secondary objective of this study was to evaluate any effects on respiration. In our study, there was no significant difference either in respiratory rate or in peripheral blood oxygen saturation (spo2) in all the three study age groups, which suggests that dexmedetomidine does not cause any respiratory depression despite, providing adequate sedation.

Richard M Venn, *et al.* [23], in their study the respiratory effects of dexmedetomidine were retrospectively examined in 33 postsurgical patients, after extubation in the intensive care unit (ICU). There were no differences in respiratory rates, oxygen saturation, arterial pH, and arterial partial carbon dioxide tension ($PaCO_2$) among the groups.

In 2011, Cooper L, *et al.* [11], did a randomized, controlled trial on dexmedetomidine to provide adequate sedation and hemodynamic control for awake, diagnostic trans esophageal echocardiography. A total of 22 Patients was randomized for standard therapy or dexmedetomidine infusion groups. They found that dexmedetomidine was equivalent in achieving adequate levels of sedation without any respiratory depression or decreasing oxygen saturation as compared with standard therapy.

Bradycardia and hypotension are the dose-dependent side effects of dexmedetomidine. In this study, we found that higher incidences of bradycardia were seen in elderly age group (23.3%) patients as compared to the middle age group (16.7%) and younger age group patients (10%), but there was no significant difference among the three age groups in comparison to mean heart rate, mean arterial blood pressure, and respiratory rate (p-value = 0.383). In 2014 Mi Hyeon Lee, *et al.* [22], during their study on 60 patients, scheduled for unilateral lower limb surgery under spinal anesthesia were randomized into three groups receiving normal saline (control group, n = 20) or 0.5 or 1.0ug/kg dexmedetomidine (D-0.5 group, n = 20; D-1, n = 20) intravenously before spinal anesthesia with 12 mg of bupivacaine, found that the RSS was significantly higher in the D-0.5 and D-1 groups than in the control group. Oxygen desaturation was not seen in any patient of dexmedetomidine groups. And there were no differences in comparison to hypotension and bradycardia among the three groups.

The present study shows that different doses of dexmedetomidine are required to achieve the same level of sedation among elderly and younger patients.

Although this study has tried to meet its aims and objectives in all aspects, there are a few limitations to it

- In the present study, we assessed the depth of sedation at the time point 26 minutes after the start of dexmedetomidine infusion, which may not represent the peak effect time in all the patients. This time point was based on the pilot testing and the previous study [10], according to that dexmedetomidine reached its peak effect around 26 minutes. Different time points are not used because repeated arousal may affect the level of sedation.
- We used different doses of the drug in the elderly in comparison to the other two groups, which may have masked some complications of the drugs.

Conclusion

The elderly patients required less amount of dexmedetomidine to achieve the same level of sedation as compared to younger patients without causing significant bradycardia, hypotension, and respiratory depression. Thus, elderly patients are more sensitive to the sedative effects of dexmedetomidine as compared to younger patients.

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